REMARKS

Claims 13, 14 and 24 have been canceled without prejudice or disclaimer. Claim 18 is amended to recite the liver tumor is a liver cancer. New Claims 34-37 have been added. Claims 18-23, 25-37 currently pending.

1. 35 U.S.C. §112, second paragraph

Claim 24 subject of this rejection has been canceled; withdrawal of the rejection is requested.

2. 35 U.S.C. §103

Applicants respectfully contest the Graham v Deere analysis of the Official Action from which the conclusion of obviousness ensues.

For ease of presentation, Applicants discuss the rejections of record in regard to the following grouping of claims: Claims 28-30, 34-37; and then Claims 18-23, 25-27, 31-33.

2.1 Claims 28-30, 34-37

For purposes of the instant discussion, the characterizing features of these claims are the "intrahepatic administration" of MMDX wherein dosage levels are "about 100 mcg/m^2 to about 1000 mcg/m^2" and the treatment is for a "human liver cancer."

As seen in the specification, this particular combination – i.e. MMDX at the specific dosage levels claimed when administered intrahepatically for treatment of a human liver cancer– results in benefits heretofore unenvisioned by the prior art. Specifically, this claimed combination of features has been discovered to enable a significant reduction in the high dosages hitherto required by IV administration without compromising the treatment regimen with the still further benefit of a dramatic and unexpected reduction in side effects, such as hematological and non-hematological toxicity.

For example, at page 11, line 27 to page 12, line 3, the instant specification reports on hematological toxicity in clinical studies performed with the invention. By way of example, it is reported that Grade 1 leucopenia was observed with the practice of the invention at dosage levels claimed. Grade 1 is understood by the artisan to be the mildest grade measure for toxic effect of chemotherapy. Moreover, the specification further relates that even non-hematological toxicity (at page 12) was generally only mild to moderate, i.e. was generally Grade 1 or 2, which grades are again indicative of the low end of toxicity.

These advantages are not foreseen by the art of record. Indeed, the art cited either makes no mention of MMDX in the context of human liver cancer –let alone the possibility that select parameters of dosage level and administration route (intrahepatically) would allow a surprising reduction in dose without sacrifice of treatment and with a tremendous lessening of deleterious side effects– or in fact suggests just the opposite.

Thus:

Bargiotti, the primary reference, discloses Compound A4, presumably MMDX. The only human biological activity offered for A4, indeed the only human data for any of the compounds generically or specifically named in Bargiotti, is at Table 6 whereat the effect of A4 on "mammary human carcinoma" using oral and IV routes is reported. Human liver cancer is unmentioned. Selectivity to liver tumors is unmentioned. Injection into the hepatic artery is unmentioned. Particular dosages for intrahepatic administration are unmentioned, including dosages of about 100 mcg/m^2 to about 1000 mcg/m^2.

Kuhl, one of the secondary references, reportedly discloses MMDX as having broad spectrum antitumor activity. But this takes us no farther than Bargiotti's overly general characterization (at col. 11, line 50) of A4 as having "antitumor activity." Kuhl examines the

effect of MMDX on human leukemia and lymphoma cell lines, only. Kuhl, like Bargiotti, does not mention use of MMDX to treat liver cancer. It does not mention selectivity to liver tumors. It does not mention hepatic artery injection. It does not mention dosage levels of MMDX for intrahepatic administration, including the levels now claimed. The Official Action takes note of Kuhl's liver activation of metabolites, the suggestion being that this somehow implicates the treatment of liver cancer. But no such inference can be fairly drawn. The liver "teaching" in Kuhl is an *in vitro* incubation of MMDX with human liver microsomes in the presence of NADPH. Applicants submit that the artisan would not make the leap from this assay to treatment of liver cancer in this context.

Nakumura teaches adriamycin (ADM) and lipidol. Adriamycin is doxorubicin. It is not MMDX. Indeed, it is decidedly not MMDX. Notable in this regard is the relation in the instant specification relates MMDX differs from ADM in that it maintains activity against doxorubicin-resistant models (page 2 lines 17-19). The Bargiotti reference, cited in the Official Action, makes the exact same observation at col. 11, lines 51-55 thereof. To equate and interchange MMDX with adriamycin as officially done is improper in the face of this clear distinction. Indeed, to do so undermines the invention and the benefits accruing to same. Moreover, while Nakumura purportedly relates the use of ADM and lipidol on certain liver cancer and conditions, it also specifically advises that no correlation between the amount of ADM (dosage) and the change in total bilirubin (ΔT-bil), a marker to evaluate ADM on the liver is found. See Section III, Results:

> "...As a result, no correlation between the amount of AMD arterially injected and ΔT-bil was found, irrespective of the existence or otherwise of cirrhosis (Figures 1 and 2)..."

This flatly belies the ability of Nakumura to presage the benefits obtained by the inventive use of MMDX at the selected dosage and administration archtypes claimed. That is, Applicants have made a correlation in relation to MMDX; Nakumura uses ADM and admits no correlation with it is found, it is thus removed at least twice over from the invention claimed.

Gorbunova teaches intrahepatic arterial infusion in certain hepatic carcinomas. Among actives used is adriamycin, at 72 hours infused at 30 $mg/m^2/24$. Adriamycin is not MMDX. See *supra*. In addition to the distinction between ADM and MMDX as noted in the instant specification and by Bargiotti, *supra*, Gorbunova provides yet another distinction. This one, however, effectively teaches away from the benefits associated with the invention. Gobunova reports toxicity for adriamycin up to level of Grade II-IV leucopenia for 50% of patients (3rd page, 4th paragraph "Regarding the toxicity..."). Compare this with the Grade 1 leucopenia resulting with the invention. Additionally, one reading Gorbunova would not only not subsequently employ MMDX at the low dosages claimed, but would instead be clearly inclined to employ increased dosages: at "Finding 2." on the last page of Gorbunova, it unequivocally states that from at least one instance described therein "suggests the possibility of increasing the total dosage and lengthening the time of intra-arterial infusion." This increase in dosage is in direct contrast to what the present Applicants have discovered and claimed with MMDX, and indeed is diametrically opposed to same.

But Gorbunova does not stop there. It continues with still other differences: clinically, Gorbunova reports "no objective responses" in a group of twelve patients with a primary inoperable hepatic carcinoma who received 17 courses of 72-hour adriamycin infusions (2nd page, 4th paragraph from bottom). This stands in stark contrast to the efficacy of the invention, where there is not only a clinical response, but one that response is far superior and

unexpected. For example, two objective tumor responses were observed at 200 mg/m^2 (see page 13, lines 9-10). This translates into a reduction of the initial tumor mass of at least 50%. Indeed, one patient evinced a complete response (Page 13, lines 14-17) from the practice of the invention.

Brem is offered by the Official Action for alleged pulse or short term administrations of chemotherapeutic agents. It thus offers no meaningful input to the above assessment and is discussed *infra*.

The claims are not obvious in view of this art, no matter how that art may be combined. None of it mentions MMDX in the context of human liver cancer. Only ADM is related in this regard by Nakumura and Gorbunova. However, ADM is art-recognized as different from MMDX for reasons *supra*, and even if *pro arguendo* one were to employ MMDX in its stead, as presumably supposed by the Official Action, one would not expect the advantages obtained at the dosage levels claimed. Indeed, in view of Gorbunova, one would reasonably expect either failure ("no objective responses") or significant toxicity (Grade 2-4 leucopenia). These features and attending results of the inventive claims are hallmarks of non-obviousness.

Applicants respectfully request withdrawal of the rejection as pertains to Claims 28-30, 34-37 and passage of same to allowance.

2.2 Claims 18-23, 25-27, 31-33

These claims either require administration of MMDX for treating human liver tumor, e.g. cancer by intrahepatic administration by infusion of from about 15 minutes to about 30 minutes every 4 weeks (Claims 18-23, 25-27, with Claim 19 to a method of reducing MMDX systemic exposure by same) or require administration as a 5 to 10 minute bolus every 8 weeks (Claim 33 akin to Claim 19).

None of Bargiotti, Kuhl, Nakumura or Gorbunova speak to these features, and the Official Action concedes as much. Which leaves us with Brem.

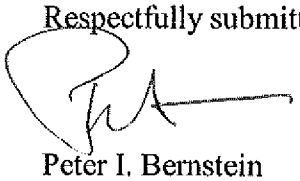
Brem relates to a delivery device for chemotherapeutic agents. It discloses use of adriamycin (ADM) in the context of gliomas, and reports that a dose-related toxicity is cardiac related. The extended release of ADM in this regard is "at least one month." The Official Action recognizes this but opines that one nonetheless be led to the treatment of liver tumors using MMDX –neither of which are disclosed– and would somehow stumble upon the short term infusion and frequency claimed, this being mere optimization.

Applicants strongly disagree. Of the art cited, only Brem relates to pulsed or short term infusions, and it does so in scenarios other that MMDX and liver cancer. Consistenly, none of the other art mentions MMDX for liver cancer. At best, the only common feature between that art and Brem is ADM, which Brem uses for gliomas at regimens officially conceded to be different from those claimed. For the reasons before stated, MMDX, is patentably distinct from ADM in the context of the present claims. See e.g. Bargiotti, and see Gorbunova, and the use of it to treat liver cancer with the benefits accrued in the context of the invention is not reasonably foreseen. To conclude that one would arrive at using MMDX for liver tumors, and then pulse the delivery thereof, as in the subject claims, on the select frequencies claimed, on the thin basis of "optimization" smacks of hindsight reconstruction. None of this is reasonably derivable from the collection of art herein.

Applicants request withdrawal of the rejection as pertains to Claims 18-23, 25-27, 31-33 with passage of same to allowance.

Applicants respectfully request favorable reconsideration as above, and offer to confer with the Examiner if convenient on the matters herein discussed.

Respectfully submitted,



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